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EXAMINER	
SWITZER, JULIET CAROLINE	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/056,908	HINKEL ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-17,19,20,23 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-17,19,20,23 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/20/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 13-17, 19-20, 23, and 31 are pending and examined herein. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

Information Disclosure Statement

2. The IDS received 5/20/02 has been considered. A signed copy of the 1449 is included with this office action.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 13-17, and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

In the instantly rejected claims, the new limitation of "to a combination of capture probes complementary to both the hybridization tag and the hybridization tab complement" in claim 13

appears to represent new matter. Applicant points to basis for this amendment at page 19, lines 13-16. This portion of the specification states that "a combination of capture probes complementary to both strands of the target polynucleotide can be used." However, this does not provide adequate basis for the instant amendment. In the portion of the specification cited, the capture probes are referring to the capture of amplified cDNA products, and the probes themselves are to be complementary to the target sequence itself. This portion of the specification is discussing a capture probe in the context of an assay for determining expression of a target polynucleotide (discussion of this method begins at ¶0037 and continues to ¶0059). This section of the specification is silent as to any discussion of hybridization tags or capture probes that are complementary to both hybridization tags and tag complements. The section of the specification beginning at ¶0060 discusses methods for SNP analysis, which is the subject of the rejected claims. The instant claims specifically state that the hybridization tag "is not complementary to the sequence containing said single nucleotide polymorphism of interest." The tag is a sequence which is introduced to the amplification product by it's attachment to the primer, it is not part of the "target sequence" that would be found in the sample. Since the capture probes discussed on page 19 are referring to capture probes for use in an entirely different method from those being used in the instant claims, this disclosure does not provide support for the newly added limitation. The examiner reviewed the specification for basis for the amendment, but was not able to identify any additional location in the specification that provides such basis. Since no basis has been identified, the claims are rejected as incorporating new matter.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 13, 14, 15, 16, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lai *et al.* in view of Fulton *et al.* (Clinical Chemistry, 43(9):1749-1756 (1997)).

This amendment has been modified to address the amendments to independent claim 13.

Lai *et al.* teach a method for detecting a single nucleotide polymorphism comprising:

(a) providing at least one primer pair, said primer pair containing a reverse primer and a forward primer comprising a 3' end specific for an allele of a single nucleotide polymorphism of interest and a hybridization tag that identifies the primer, said hybridization tag not complementary to the sequence containing said single nucleotide polymorphism of interest (¶ 0179);

(b) combining said at least one primer with a sample containing single-stranded polynucleotides under stringent conditions which allow hybridization of said primers to complementary sequences in said single-stranded polynucleotides (¶ 0179);

(c) extending hybridized primers by primer extension to produce an extension product wherein said extension product comprises said hybridization tag and a hybridization tag complement, and a detectable label (¶ 0179; see also Figure 5);

(d) hybridizing said extension products by said hybridization tag or the complement thereof under stringent conditions to capture a probe wherein said capture probe is coupled to a microbead, said microbead identifying said capture probe (¶0181, ¶ 0182);

(e) detecting the hybridization of said extension product to said capture probe by the presence of said detectable label (¶ 0182); and

(f) determining the identity of said single nucleotide polymorphism based on the identity of said particle (¶ 0182).

With regard to claim 14, Lai *et al.* teach that the reverse primer comprises a detectable label (¶ 0179).

With regard to claim 15, Lai *et al.* further teach that the reverse primer is a universal primer that is universal to both alleles being tested (¶ 0185, also figure 12).

With regard to claim 16, Lai *et al.* teach repeating the extension step in subsequent rounds of PCR (¶ 0180).

With regard to claim 17, Lai *et al.* teach that this assay can be multiplexed, thus comprising a plurality of primer pairs specific for a plurality of single nucleotide polymorphisms (¶ 0183).

Lai et al. teach at least two methods for labeling the extension products, one which is depicted in the drawings where a labeled primer is used, but also an additional method where labeled nucleotides are included in the PCR reaction (see for example ¶40 and ¶84). In such an embodiment, both strands of the amplification product would contain the labeled nucleotides.

Lai *et al.* do not teach a method wherein the capture probes comprise probes complementary to both the tag and the tag complement, nor do Lai et al. teach a method wherein detection is by flow cytometry. (For clarity of the record, it is noted that Lai *et al.* at ¶ 0264 do teach detection by flow cytometry. However, this disclosure is not supported by Lai *et al.*'s provisional application, which support is relied upon in this rejection).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, however, to have modified the methods taught by Lai et al. so as to have included capture probes to both the tag and the tag complement. One would have been motivated to do so for use with the embodiment of Lai et al. that teaches the inclusion of labeled nucleotides in the PCR reactions, which would have resulted in the labeling of both nucleic acid amplification product strands. In such an embodiment, one of skill in the art would have been motivated to include capture probes for both labeled strands, with the expected benefit of increasing the detection signal by capturing twice the number of amplified strands of nucleic acid.

Fulton *et al.* teach methods of sorting and detecting microspheres which utilize flow cytometry, and in particular teach these methods in conjunction with nucleic acid hybridization methodologies (p. 1753-1755). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Lai *et al.* so

as to have included a flow cytometry step for the detection of hybridization of the extension product, as taught by Fulton *et al.*, including any necessary modification of the beads taught by Lai et al. necessary for the practice of the flow cytometry methods taught by Fulton et al. One would have been motivated to utilize such methodology because Fulton *et al.* teach that their system "represents a revolutionary new technology that can be applied to virtually any application that requires analysis of molecular interactions..." and that their system "...is unique in its ability to provide multiplexed, high-throughput analysis coupled with real-time data analysis..." offering "excellent sensitivity, precision, speed, and economy (p. 1775)." Thus, one would have been motivated to use the flow cytometry based methods taught by Fulton et al. to detect alleles as taught by Lai *et al.* in order to take advantage of such a system as taught by Fulton *et al.*

8. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lai *et al.* in view of Fulton *et al.*, as applied to claims 13, 14, 15, 16, 17, 20, and 23 in the previous rejection, and further in view of Wallace *et al.* (WO 93/25563).

The teachings of Lai *et al.* in view of Fulton *et al.* are described in the previous rejection.

With regard to claim 19, Lai *et al.* in view of Fulton *et al.* do not teach the application of this methodology for diagnosing a disease, condition, disorder or predisposition. However, at the time the invention was made, it was routine in the prior art to utilize the detection of single nucleotide polymorphisms for the detection of any number of diseases. For example, Wallace *et al.* teach the detection of diseases such as sickle cell anemia or thalassemia caused by a defective allele (p. 5, first full paragraph). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have utilized the methods taught by Lai *et al.* in

view of Fulton *et al.* for the detection of disease as suggested by Wallace *et al.* in order to have provided a method for detecting diseases caused by single nucleotide polymorphisms.

9. Claims 20, 23, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang *et al.* in view of Fulton *et al.*

This rejection is modified to address the amendments to independent claim 20.

With regard to claim 20, Huang *et al.* teach a method for detecting a single nucleotide polymorphism comprising:

a) providing at least one a group of at least 2 primers in each group, wherein each primer comprises a hybridization tag that identifies said primer, and each primer in said group having a 3' end specific for a different allele of a single nucleotide polymorphism of interest (Col. 2, lines 50-55; Col. 4, lines 20-25; Col. 17, lines 55-60; Claim 15);

b) combining said at least one primer with a sample containing single stranded polynucleotides under stringent conditions which allow hybridization of said primer to complementary sequences in said single-stranded polynucleotides (Col. 2, lines 45-50);

c) extending hybridized primers by multi-base primer extension to produce an extension product, said extension product comprising said hybridization tag and a detectable label (Col. 2, lines 55-57; Col. 8, line 55 which teaches primers are extended by "one or more labeled nucleotides," which is a clear teaching of a multi-base extension);

d) hybridizing said extension product by said hybridization tag under stringent conditions to a capture probe, said capture probe coupled to a particle that identifies said capture probe (Col. 2, lines 57-59);

e) detecting the hybridization of said extension product to said capture probe using said detectable label (Col. 4, lines 14-16);

f) determining the identity of said single nucleotide polymorphism based on the identity of said particle (Col. 5, lines 43-52).

Huang *et al.* teach that this assay can be multiplexed, thus comprising a plurality of primers specific for a plurality of single nucleotide polymorphisms (Col. 4, lines 20-25). Huang *et al.* teach a method wherein said at least one primer comprises a group of at least 2 primers, each primer specific for a different allele of a single nucleotide polymorphism of interest (Col. 17, lines 55-60; Claim 15).

With regard to claim 23, Huang *et al.* teach a method further comprising a plurality of said primer groups, each primer group specific for a different single nucleotide polymorphism of interest (Col. 4, lines 20-25).

With regard to claim 31, Huang *et al.* teach that their methods can be employed to detect mutations and identify phenotypes of mutations in clinical diagnostics and clinical studies (Col. 7, lines 25-30).

Huang *et al.* teach that the solid support can be beads (Col. 5, line 46, and claim 7), but they do not teach a fluorescent microbead.

Huang *et al.* do not teach a method wherein the detection is by flow cytometry.

Fulton *et al.* teach methods of sorting and detecting microspheres which utilize flow cytometry, and in particular teach these methods in conjunction with nucleic acid hybridization methodologies (p. 1753-1755). Fulton et al. expressly teach the use of fluorescent microbeads (p. 1750, 2nd column, heading "*Microspheres*"). It would have been prima facie obvious to one

of ordinary skill in the art at the time the invention was made to have modified the methods taught by Huang *et al.* so as to have included a flow cytometry step for the detection of hybridization of the extension product, as taught by Fulton *et al.* so as to have included a flow cytometry step for the detection of hybridization of the extension product, as taught by Fulton *et al.*, including any necessary modification of the beads taught by Huang et al. necessary for the practice of the flow cytometry methods taught by Fulton et al. One would have been motivated to utilize such methodology because Fulton *et al.* teach that their system "represents a revolutionary new technology that can be applied to virtually any application that requires analysis of molecular interactions..." and that their system "...is unique in its ability to provide multiplexed, high-throughput analysis coupled with real-time data analysis..." offering "excellent sensitivity, precision, speed, and economy (p. 1775)." Thus, one would have been motivated to use the flow cytometry based methods taught by Fulton et al. to detect alleles as taught by Huang *et al.* in order to take advantage of such a system as taught by Fulton *et al.*

Response to Remarks

Applicant argues at page 8 that the rejection of claim 13 under Lai et al. in view of Fulton et al. is not proper because Lai et al. does not teach hybridization to a combination of capture probes complementary to both the hybridization tag and the complement thereof. This amendment has been addressed in the newly set forth 103 rejection. The remarks regarding Lai et al. in view of Fulton et al. and further in view of Wallace et al. also rely on this supposed deficiency in Lai et al. which has been addressed in the rejection. The rejection is modified and maintained.

Applicant argues on page 16 that the rejection under Huang et al. in view of Fulton et al does not recite a capture probe coupled to a fluorescent microbead. However, this is not persuasive because Fulton et al. expressly teaches fluorescent microbeads. The rejection is modified to address the amendment and maintained.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Thursday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Juliet C. Switzer
Primary Examiner
Art Unit 1634

July 13, 2006